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Application No. : **2,413,711**
Owner : VERTEX PHARMACEUTICALS (SAN DIEGO) LLC
Title : **ION CHANNEL ASSAY METHODS**
Classification : G01N 33/483 (2006.01)
Your File No. : **60209-31**
Examiner : Jesse McDaniel

YOU ARE HEREBY NOTIFIED OF A REQUISITION BY THE EXAMINER IN ACCORDANCE WITH SUBSECTION 30(2) OF THE *PATENT RULES*. IN ORDER TO AVOID ABANDONMENT UNDER PARAGRAPH 73(1)(A) OF THE *PATENT ACT*, A WRITTEN REPLY MUST BE RECEIVED WITHIN **6** MONTHS AFTER THE ABOVE DATE.

This application has been examined taking into account the:

Description, pages 1-105, as originally filed;
Claims, 1-48, as originally filed; and
Drawings, pages 1/35 - 35/35, as originally filed.

This application has been examined taking into account applicant's correspondence on prior art received in this office on March 17, 2006, November 2, 2006, and October 26, 2007.

The number of claims in this application is 48.

The search of the prior art has revealed the following:

References Applied:

PCT Application

WO 96/41166 □	19-2-1996	G01N 33/50	Tsien et al.
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Publications

Drug Discovery Today □	Sept. 1999	4(9):431-439	Gonzalez et al.
Biophys J.	March 1996	70(3):1347-62	Fishler et al.
Biophys J.	Aug. 1986	50(2):339-48	Gross et al.

□ citation stemming from a foreign search report

Tsien et al., herein referred to as D1, disclose methods and compositions for determining the potential of a membrane.

Gonzalez et al., herein referred to as D2, disclose cell-based assays and instruments for screening ion-channel targets.

Fishler et al., herein referred to as D3, disclose mechanisms by which extracellular electrical field stimuli induce cardiac cell excitation.

Gross et al., herein referred to as D4, disclose imaging of spatial distributions of transmembrane potential changes induced in non-excitabile cells by applied electric fields.

The examiner has identified the following defects in the application:

Claims 1, 21, 30, and 41 define subject matter which cannot operate, and therefore do not comply with section 2 of the *Patent Act*. There is no step that defines how to monitor/detect changes in the transmembrane potential of one or more cells. The methods defined in the claims therefore lack utility.

Claims 1-44 do not comply with section 28.3 of the *Patent Act*. The subject matter of these claims would have been obvious on the claim date to a person skilled in the art or science to which they pertain having regard to D1 or D2 in view of D3.

D1 and D2 teach a method for determining the potential of a membrane by measuring energy transfer between a fluorescent ion and a chromophore when they are excited by a light source. Said energy transfer is typically measured by fluorescence resonance energy transfer (FRET). In a further embodiment a method of screening potential therapeutic drugs which affect the membrane potentials of cells is disclosed. Further the use of recombinant cells, into which ion channels have been expressed by genetic engineering, and the use of ion channel blocking is disclosed. Ion channels of interest include sodium, calcium, and potassium which may be voltage-gated or ligand-gated.

While D1 and D2 teach an optimal stimulus of membrane potential (D1 - pg 43:line4 and D2 - pg 437:line 13), they do not teach the specific use of a monophasic or biphasic electric field in detail. D3 teaches the use of such fields to induce the excitation of cardiac cells. Responses were generated for rectangular monophasic and symmetric biphasic field stimuli of 2-20 ms total duration.

Therefore, it would have been obvious to one skilled in the art to interchange the stimulus disclosed in D1 and D2 with that of an externally applied electric field. Further the use of optical imaging of cell membrane potential, by FRET as well as other methods, genetically expressing ion channels in cells, and means of high volume drug screening were known in the art.

Claims 30-40 do not comply with paragraph 28.2(1)(b) of the *Patent Act* because these claims include subject matter disclosed in D4 before the claim date.

D4 teaches the optical imaging of cell membrane potential changes induced by applied electric fields. Changes are indicated by the fluorescence intensity of a charge shift potentiometric dye, di-4-ANEPPS, incorporated in the cell membrane. Four cell types were tested: A-431 human carcinoma cells, rat basophilic leukemia (RBL) cells, spores of a fungus, and protoplasts isolated from the root crown tissue of rye.

Claims 45-48 do not comply with paragraph 28.2(1)(b) of the *Patent Act*. D3 disclosed the claimed subject matter before the claim date. The teachings of D3 are discussed above.

Claims 6, 7, 13, 16, 32, 42, and 48 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The second introduction (use of an indefinite article) of an element already introduced causes ambiguity. The terms:

- "an ion channel of interest" (claim 6, line 1)
- "an ion channel of interest" (claim 7, line 1)
- "an area of observation" (claim 13, line 2)
- "an amplitude" (claim 16, line 2)
- "a FRET based voltage sensor" (claim 32, line 1)
- "a transmembrane potential change" (claim 42, line 1)
- "a rate" (claim 48, line 1)

have been defined previously in the claims. The aforementioned terms should therefore be referred to using a definite article.

Claims 11-13, 17-20, 41-43, and 47 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. The following terms have no antecedents:

- "said electric field" (claim 11, line 1)
- "the area of observation" (claim 11, line 2)
- "the mean electric field" (claim 12, line 2)
- "the mean electric field" (claim 13, line 2)
- "the transmembrane time constant" (claim 17, line 2)
- "said transmembrane potential" (claim 20, line 1)
- "said ion channel of interest" (claim 42, line 2)
- "said ion channel of interest" (claim 43, line 1)
- "said pulse duration" (claim 47, line 1)

Claims 1 and 30 are indefinite and do not comply with subsection 27(4) of the *Patent Act*. Claims containing a negative expression such as "without using a patch clamp" is objectionable in that claims should generally set forth what the invention is or does, and not what it is not or does not do.

In accordance with subsection 81(2) of the *Patent Rules*, all documents referred to in the description of an application must be available to the public. Reference to the documents on page 1, lines 4-9 must be deleted or replaced by their corresponding patent numbers or publication numbers.

Under section 34 of the *Patent Rules*, any amendment made in response to this requisition must be accompanied by a statement explaining the nature thereof, and how it corrects each of the above identified defects.

In view of the foregoing defects, the applicant is requisitioned, under subsection 30(2) of the *Patent Rules*, to amend the application in order to comply with the *Patent Act* and the *Patent Rules* or to provide arguments as to why the application does comply.

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Patent Examiner
819-934-5173

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